

Ageing microenvironment mediates lymphocyte carcinogenesis and lymphoma drug resistance: From mechanisms to clinical therapy (Review)

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Abstract. Cellular senescence has a complex role in lymphocyte carcinogenesis and drug resistance of lymphomas. Senescent lymphoma cells combine with immunocytes to create an ageing environment that can be reprogrammed with a senescence-associated secretory phenotype, which gradually promotes therapeutic resistance. Certain signalling pathways, such as the NF- κ B, Wnt and PI3K/AKT/mTOR pathways, regulate the tumour ageing microenvironment and induce the proliferation and progression of lymphoma cells. Therefore, targeting senescence-related enzymes or their signal transduction pathways may overcome radiotherapy or chemotherapy resistance and enhance the efficacy of relapsed/refractory lymphoma treatments. Mechanisms underlying drug resistance in lymphomas are complex. The ageing microenvironment is a novel factor that contributes to drug resistance in lymphomas. In terms of clinical translation, some senolytics have been used in clinical trials on patients with relapsed or refractory lymphoma. Combining immunotherapy with epigenetic drugs may achieve better therapeutic effects; however, senescent cells exhibit considerable heterogeneity and lymphoma has several subtypes. Extensive research is necessary to achieve the practical application of senolytics in relapsed or refractory

lymphomas. This review summarises the mechanisms of senescence-associated drug resistance in lymphoma, as well as emerging strategies using senolytics, to overcome therapeutic resistance in lymphoma.

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1. Introduction

Cell senescence is a process that permanently arrests cellular proliferation, which not only triggers tissue remodelling during organismal development and after body injury but also leads to inflammation, tumorigenesis and decreased regenerative function of tissues (1-3). Cellular senescence is classified into the following types: i) Replicative senescence; ii) stress-induced premature senescence (SIPS), including DNA damage- and oxidative stress-induced senescence; iii) oncogene-induced senescence (OIS); iv) paracrine senescence; v) therapy-induced senescence (TIS); vi) mitochondrial dysfunction-associated senescence; and vii) epigenetically induced senescence (3,4).

Although cell senescence is generally considered beneficial, malignancy is also associated with senescence, both of

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which are caused by accumulation of time-dependent cellular damage (5). Senescent cells can secrete cytokines [including interleukin (IL)-6, IL-8, tumour necrosis factor (TNF) α and interferon-(IFN) γ], chemokines [C-C motif ligand 2 and C-X-C motif chemokine ligand (CXCL)1], growth factors (granulocyte-macrophage colony-stimulating factor) and matrix metalloprotein (matrix metalloproteinase 9), into the ageing environment and gradually induce a senescent-associated secretory phenotype (SASP) (6,7). In tissues, the short-term accumulation of aged cells is beneficial for renewing the *in vivo* environment; however, the long-term accumulation of aged tumour cells may induce disequilibrium in an organism or local organs and gradually result in the formation of an aged tumour microenvironment (TME) (8). Among lymphatic system malignancies, lymphoma development, including histopathology, clinical treatment and prognosis, differs between young and old adults (9). In Hodgkin's lymphoma (HL), Reed-Sternberg (RS) cells retain the characteristics of senescent cells, staining specifically for senescence-associated β -galactosidase (SA- β -gal) and exhibiting abnormal expression of cell cycle inhibitors p21^{Cip1}/p16^{INK4a}/p53, and negative Ki-67 expression. In addition, RS-like cells exhibit a SASP in their microenvironments (10).

Drug resistance is one of the main challenges encountered by clinicians in lymphoma treatment. When treated with a single drug, tumours can resist multiple chemically unrelated drugs, resulting in multidrug resistance (MDR) (11). Common factors involved in MDR include: i) Expression of efflux transporters, such as P-glycoprotein [P-gp; also called ATP binding cassette subfamily B member 1 (ABCB1)], ATP binding cassette subfamily G member 2 [ABCG2, breast cancer resistance (BCR) protein], and multidrug resistance-associated protein 1. P-gp, encoded by *MDR1*, has a crucial role in lymphoma multidrug resistance (12). Anthracycline resistance is mediated by the overexpression of P-gp, a transmembrane protein that functions as an efflux pump, actively transporting anthracyclines out of cancer cells, thereby reducing their intracellular concentration and efficacy (13). ii) Tumour stem-like cells (also known as side populations) (14). However, the additional mechanisms underlying lymphoma resistance remain to be explored. Hanahan (15) reported that tumour cells undergo transient ageing in cases of therapeutic resistance. These senescent tumour cells appear dormant and evade targeted drug attacks (16). In such cases, SASP have a crucial role in the development of lymphoma resistance (17). In murine models of Burkitt's lymphoma, DNA damage has been found to induce the release of paracrine factors [such as IL-6 and metalloproteinase tissue inhibitor 1 (Timp-1)], which contribute to lymphoma cell survival in the TME after chemotherapy and create a 'chemoresistant niche' (18). These studies suggest that the ageing microenvironment, in which the SASP is involved, may have a critical role in the mechanisms of chemotherapy resistance in lymphoma.

The present review, from the perspective of preclinical research and clinical applications, focuses on the interactions between the ageing TME and lymphocyte carcinogenesis and discusses how the ageing microenvironment is reprogrammed and promotes the development of lymphoma resistance. Finally, opportunities and challenges in solving the problem

of drug resistance in lymphoma were discussed from the perspective of an ageing microenvironment.

2. The ageing microenvironment mediates lymphocyte carcinogenesis

B-cell-derived lymphoma. The expression of SASP markers, such as cytokines TNF- α /IL-6/IL-8 and microRNA-155, -16 and -93, have been detected in memory B cells (19). Compared to young mice, older mice showed considerable differences in B-cell composition in lymphatic tissues. This part of the B lymphocyte lineage is termed age-associated B cells, which secrete TNF- α and suppress pro-B-cell survival and B lymphopoiesis (20,21).

T cell-derived lymphoma. Changes in the ageing host and senescent cell metabolism can seriously affect T-cell development, maintenance and function (22). For instance, T cells expressing T cell immunoglobulin and mucin domain-containing protein 3 include a subset of senescent cells arrested in the G1/S phase (23). In old mouse models, memory CD8⁺ T cells with CD44^{low}CD62L^{high} express high levels of stem cell antigen-1 (24,25). Furthermore, $\gamma\delta$ T-cells exert the function of killing lymphoma cells in the TME. However, in an ageing microenvironment, a large number of changes in the composition of the $\gamma\delta$ T-cell pool in peripheral lymph nodes (pLNs) may lead to an imbalance of $\gamma\delta$ T-cell responses in tumours and accelerate tumour growth. Ageing alters the function of the T cell receptor δ chain and the clonal structure of $\gamma\delta$ T-cell subsets. In old mice, increased IL-7 expression mediates the expansion of the $\gamma\delta 17$ T-cell compartment, which is related to lymphoma growth (26). Furthermore, human type 17 T-helper (Th17) cells possess stem cell-like properties and intervention with Th17 stemness may help address Th17-associated drug resistance, microenvironmental disturbances and organ disabilities (27). Failure of the T-cell metabolism leads to the accumulation of circulating cytokines that act as systemic inducers of ageing. Immune dysregulation ultimately leads to T cell-derived lymphoid tissue neoplasms (28).

Natural killer (NK) cell-derived lymphoma. There is a close relationship between abnormal NK-cell function, carcinogenesis and the ageing microenvironment. A key feature of NK cells is the expression of human leukocyte antigen class I-specific receptors, which manifests as the downregulation of NK group 2A (NKG2A) receptor and upregulation of killer cell immunoglobulin-like receptor (KIR) family members. However, the ageing microenvironment affects the function and phenotype of KIR/NKG2A repertoires, which cause abnormal or cancerous functions in NK cells (29). In addition, NK cells from patients with germline gain-of function mutations in PIK3CD (encoding the PI3K p110 δ catalytic subunit) exhibit abnormal differentiation, which is associated with the overexpression of immunosenescence/depletion-related markers. Immunosenescence may lead to a decline in the ability of the immune system to monitor and clear abnormal cells, thus providing a more favourable environment for NK cells to become cancerous (30). In summary, the complex mechanism between NK-cell cancer and the immunosenescent

microenvironment needs to be further explored, as it is crucial for the treatment and prevention of NK cell-derived lymphoma.

3. Biomarkers of senescence-mediated lymphoma resistance

Senescent cells are heterogeneous at different stages of cancer (31). Researchers have often combined senescent cells, drug resistance and tumour stem cell markers to study ageing-induced drug resistance. Biomarkers of senescent cells in lymphoma require further investigation. In this chapter, the biomarkers of senescent lymphoma cells that have been reported to date are discussed.

SA- β -gal. SA- β -gal is widely recognised as a critical biomarker for senescent cells, including lymphoma. Milanovic *et al* (32) selected SA- β -gal and 5-bromo-2'-deoxyuridine/propidium iodide (BrdU/PI) as markers to analyse senescent cells with stemness in B-cell lymphoma in both human cell lines and mouse models. Senescent lymphoma cells were detected by SA- β -gal staining in the ageing environment of relapsed or refractory (R/R) diffuse large B-cell lymphoma with elevated expression of the SENEX gene (33). SA- β -gal expression is important in the study of drug resistance mechanisms, as it allows researchers to identify whether cellular senescence has been induced and understand how senescent lymphoma cells resist treatment, which may potentially be applied in lymphoma treatment.

SASP. The SASP has a critical role in lymphoma progression, enhances pro-cancerous effects on surrounding lymphoma cells and tissues via paracrine and autocrine pathways, and may affect the immune response in human cell lines and mouse models (34). SASPs act as both promoters and inhibitors of lymphoma development. Certain SASP components promote tumour-cell formation and development; however, other components may have a role in the immune response, helping to fight cancer cells. All these functions of the SASP components depend on the antitumour drug action time, drug intensity and immune microenvironment of the organisms involved. The relationship between SASP and lymphoma is a complex area of research and scientists are working to develop new treatments or intervention strategies to improve treatment outcomes in lymphoma cases involving drug resistance (35).

Suppressor of variegation 3-9 homolog 1 (SUV39H1). Trimethylation of histone H3 lysine 9 (H3K9me3) and the H3K9me3-specific histone methyltransferase SUV39H1 have been reported as biomarkers for senescent lymphoma cells in human cell lines and mouse models (36). H3K9me-mediated ageing blocks the response to the oncogene *Ras*. Loss of SUV39H1 activates *Ras* expression and enhances lymphoma aggressiveness (36). In addition, TIS relies on SUV39H1, which promotes lymphoma (37). Overexpressed *MYC* is a well-known lymphoma oncogene that can induce self-renewal of stem cells and prevent cell differentiation (38-40). The function of *MYC* is limited by TGF- β regulation and the development of lymphoma is inhibited by SUV39H1-dependent cellular senescence (41).

RAS. RAS represents a class of signalling proteins belonging to the small GTPase family and includes various subtypes, such as H-RAS, K-RAS and N-RAS (42). RAS proteins have key regulatory roles in normal cell growth and development; however, aberrant RAS signalling pathway activity has been implicated in various tumours and other diseases. RAS is also involved in the regulation of cellular senescence in human cell lines and mouse models (43-45).

Patients with high expression of the *RAS* oncogene (also termed *K-RAS*) have a poor prognosis and often exhibit MDR (46). RAS is the most common marker used in studies of lymphoma OIS. It is regulated by another important senescence-associated biomarker, SUV39H1, and drives cell-cycle arrest, which exacerbates the promalignant paracrine activity of the SASP, confirming the core feature of genotoxic stress-induced senescence (36). In general, the RAS signalling pathway is involved in the regulation of cellular senescence, which is essential for understanding the occurrence and development of drug resistance in lymphoma (47).

ABC protein family. The ABC protein family is closely associated with drug resistance in tumours. Lymphoma stem-like cells (CD34⁺ and CD44⁺) with high ABCG2 expression exhibited a senescent phenotype in mouse models (37). Multidrug resistance protein 4 (ABCC4) is overexpressed in human NK/T-cell lymphoma (NKTCL) cells, which modifies the sensitivity of chemotherapy to epirubicin and cisplatin and may be a functional therapeutic target (48). In senescent cells, ATP-binding box subfamily B member 4 mediates the synthesis and release of small extracellular vesicles and enhances drug resistance in cancer cells (49). ABCA1 participates in the export of free cholesterol by specific cells, such as macrophages and foam cells, into the lymphoma microenvironment, which in turn promotes lymphoma cell proliferation (50). ABCG2 enhances the multidrug resistance profile of human NKTCL side-population cells (51). Thus, ABC protein family members combined with senescence-associated biomarkers (e.g. SA- β -gal), may be used as indicators to evaluate senescence-related drug-resistant traits.

4. Signal transduction pathways in senescence-mediated lymphoma resistance

The relationship between senescence and lymphoma resistance involves complex signalling pathways. It should be noted that lymphomas are a group of highly heterogeneous diseases; thus, different molecular subtypes and individual idiosyncrasies may have different regulatory mechanisms involving their signalling pathways. Therefore, the mechanisms underlying the signalling pathways involved in cellular senescence in lymphoma must be studied in depth according to specific lymphoma subtypes. Certain key signalling pathways that may have critical roles in senescence-related lymphoma resistance were discussed in the following sections.

P53/NF- κ B signalling. The SASP depends on paracrine mechanisms involving interleukins IL-6 and IL-8 to induce epithelial-mesenchymal transition and aggressive malignancy. Loss of p53 exacerbates the paracrine activity of the SASP (47). Proteomic analyses have identified NF- κ B as a

critical regulator of SASP in senescent chromatin. Subunit p65 of NF- κ B is a major transcription factor and accumulates on senescent chromatin. NF- κ B inhibition triggers escape from immune recognition by NK cells and bypasses the senescence mechanism by collaborating with inactivated p53. In mouse lymphoma models, NF- κ B inhibition alters the microenvironment of treatment-induced senescence by controlling SASP, promoting drug resistance and early recurrence of lymphoma, and shortening survival time (17). In HL, RS cellular senescence with abnormal expression of SA- β -gal and p21^{Cip1}/p16^{INK4a}/p53 may also be the origin of the pro-inflammatory microenvironment and gradual development of SASP and promote HL drug resistance. NF- κ B inhibitors (such as JSH-23 and curcumin) decrease the secretion of IL-6 from RS-like cells in HL (10).

Wnt signalling. The Wnt signalling pathway has a critical role in cell fate determination and differentiation. In senescent lymphoma cells, the aberrant activation of Wnt signalling may lead to the maintenance of a stem cell-like state, inhibiting normal cell differentiation. Abnormal Wnt/ β -catenin signalling promotes tumour stem-like cell proliferation and thus has a critical role in tumour resistance and treatment responses (52). Wnt signalling has been reported to participate in the SASP-mediated proliferation of stem-like cells in the B-cell lymphoma SASP (32). The application of Wnt protein pathway inhibitors can potentially enable more precise and personalised treatment of drug-resistant lymphoma.

MAPK signalling. Extracellular signal-regulated protein kinases (ERK), such as ERK1 and ERK2, act on cytotoxic T cells (CTLs) and participate in IFN-mediated resistance of T lymphoma cells (53). Furthermore, numerous aneuploid senescent cells often exist as double-hit or double-expressing diffuse large B-cell lymphomas (DH/DE-DLBCLs) after treatment. This mechanism of mitotic escape leads to drug resistance. These aneuploid senescent cells increase ERK/MAPK activity via Bruton's tyrosine kinase (BTK) signalling and the chronically active BCR pathway, resulting in elevated metabolism (54).

PI3K/AKT/mTOR signalling. The PI3K/AKT/mTOR pathway is a potent cell proliferation and growth signalling pathway that is also involved in the regulation of the cell cycle and apoptosis. In lymphoma, overactivation of this pathway is frequently observed under repeated stress conditions, leading to abnormal cell proliferation (55,56). Senescent cells escape the treated DH/DE-DLBCL microenvironment and acquire improved metabolic properties via the AKT/mTOR pathway, resulting in drug resistance (54). Downregulation of this pathway may help to restore the apoptotic capacity of cells and regulate the cell cycle, thereby inhibiting lymphoma-cell proliferation.

Notch signalling. In lymphoma, the aberrant activation of the Notch signalling pathway is closely associated with disease onset and progression. In senescent lymphoma cells, Notch signalling cascades with fibroblast growth factor and Wnt signalling to maintain self-renewal of tumour stem cells and remodel the TME (57). Currently, research on the mechanism of action of Notch in lymphoma-cell senescence is expanding, and future studies will help to reveal the underlying molecular mechanisms in greater detail.

JAK-STAT signalling. The JAK-STAT signalling pathway is a key pathway involved in cell proliferation, differentiation and immune responses. Senescent lymphoma cells may evade detection and attack by the immune system by manipulating the JAK-STAT signalling pathway (58). The JAK/3 signalling pathway is required for lymphoma cell survival after doxorubicin (DOX) treatment *in vivo* and *in vitro* (18). Certain cytokines have a role in JAK-STAT signalling. IL-15 stimulates JAK3-STAT5 signalling and inhibits the expression of DNA damage response genes, thus delaying CD8+ T-cell senescence (59). IL-6 reverses DOX resistance in nasal NKTCL by downregulating ABCC4 and inactivating the JAK2/STAT3/NF- κ B/P65 pathway (Fig. 1) (60). Therefore, inhibition of the JAK-STAT pathway by interfering with the expression of SASP to kill drug-resistant lymphoma cells with a senescent phenotype is a promising direction for future research.

5. Research model applications in senescence-associated lymphoma resistance

Cell and animal models have revealed several mechanisms through which senescent cells develop drug resistance, facilitating the development of additional senolytic drugs based on these models. Different types of senescence have been observed in various cellular and animal models. In this chapter, various research models for lymphoma senescence-associated resistance are discussed.

Cell models. For TIS, the induction time has a critical role for constructing cell models of lymphoma senescence-associated resistance. In clinical patients, after completion of a cancer treatment regimen, TIS in tumours and normal tissues can gradually develop within 10 days to 6 weeks (31). In an *in vitro* assay, tumour cell lines treated with various chemotherapeutic drugs were used as cell models to study senescence-associated resistance. The senescent phenotype can be identified via SA- β -gal assays and SASP-related cytokine detection (such as IL-4, IL6, IL-1 β) (61). One study reported that β -gal-positive cells could be induced in non-small cell lung cancer cell lines after 2-6 days of treatment with cisplatin (62). To date, limited research has been conducted on TIS-cell lymphoma models.

Animal models. For SIPS, excision repair cross complement 1 knockout/deletion mice have been used as a DNA-damaging model to study senolytic drugs (63,64). In OIS, BUB1 mitotic checkpoint serine/threonine kinase B (BubR1) encodes a vital component of mitotic spindle assembly. The BubR1H/H mouse is an ideal model of cellular senescence (63,65). Mdr2^{-/-} mice treated with navitoclax (ABT263) are good models for primary lymphoma resistance research (66). Telomerase knockout mice are ideal models for studying senescence-associated mechanisms of immune escape (67). In the case of TIS, primary E μ -Myc transgenic Bcl2-overexpressing lymphomas treated with adriamycin are a recognised mouse model for the study of TIS of B-cell lymphoma. SUV39H1 inhibits the conversion of normal cells into induced pluripotent stem cells. SUV39H1-deficient E μ -Myc mice have been demonstrated to be a suitable model of senescence-associated resistance in B-cell lymphoma (32,68).

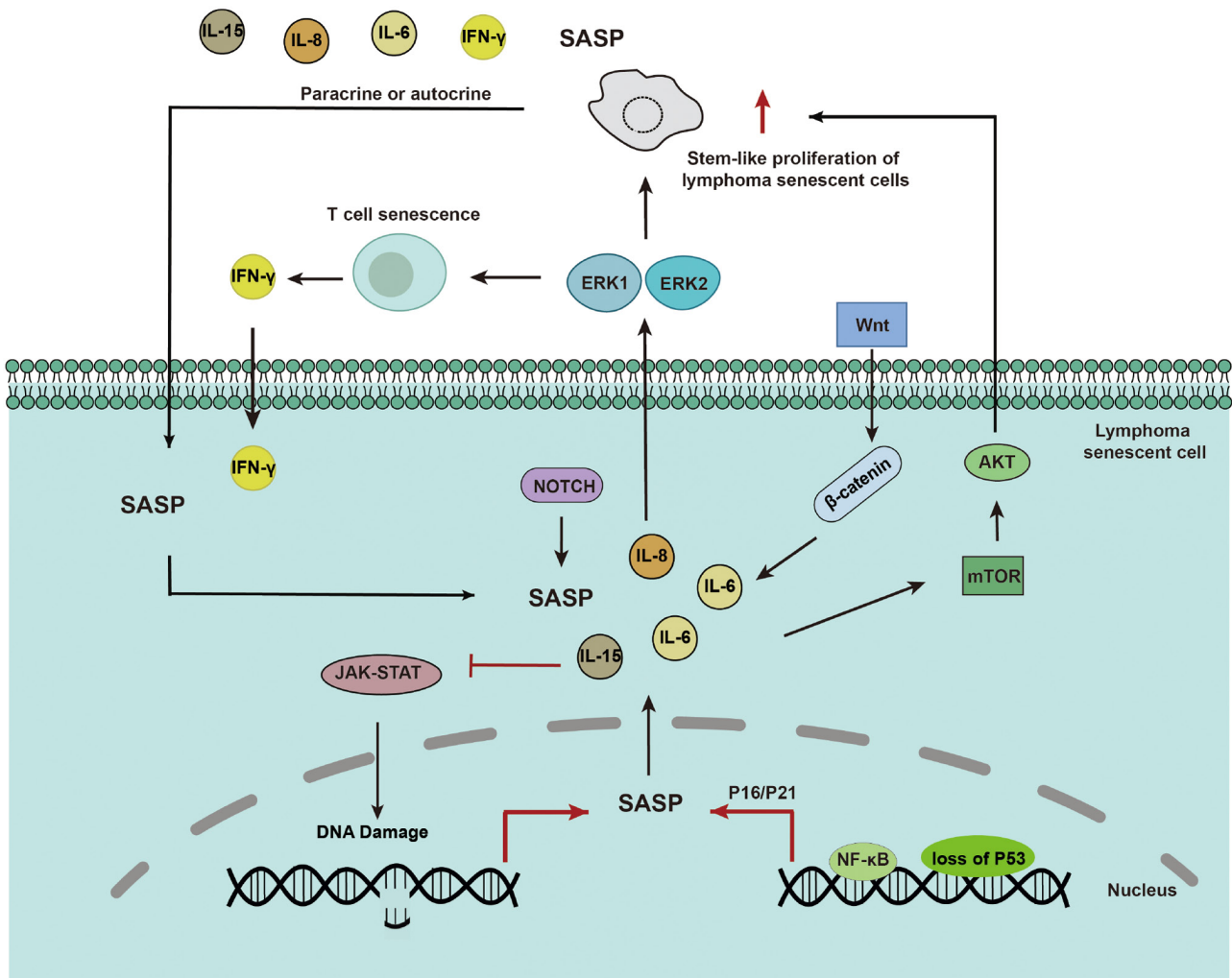


Figure 1. Main signalling pathway mechanisms of SASP in lymphoma cellular resistance. The loss of p53 and expression of NF-κB exacerbate the paracrine activity of SASP, which promotes cytokine secretion, as well as signal transduction pathways, including mTOR/NOTCH/ERK/JAK-STAT, mediate the stem-like proliferation of lymphoma senescent cells. All of these facilitate the drug resistant characteristics of lymphoma cells. SASP, senescent-associated secretory phenotype.

In one study, a patient-derived DLBCL xenograft model (PDX) was successfully established to screen for drug sensitivity and explore resistance mechanisms (69). Cell-derived mouse xenograft models have been frequently used to study the mechanisms underlying drug-resistant lymphoma (70).

Three-dimensional (3D) organoid models. Multiple lymphoid organs have been designed in the field of immune engineering, such as the engineering of bone marrow and thymus tissue (71). The lack of understanding of the factors that regulate lymphoma resistance and the establishment of predictors is mainly due to the need for *in vitro* lymphoma models to accurately study the lymphoma microenvironment. In contrast to other tumour types, the development of lymphoma organoids is slow (72).

Tian *et al* (72) established a synthetic hydrogel 3D organoid microenvironment for B- and T-cell lymphomas using biomaterials such as maleimide-functionalised 4-arm polyethylene glycol and thiolated cross-linkers, which could effectively detect drug sensitivity and resistance. Of note, B-cell lymphoma cell lines (HBL-1, DOHH2, WSU-DLCL-2,

SUDHL-4, SUDHL-6, OCI-Ly10 and OCI-Ly12) and a T-cell lymphoma cell line (HuT-78) were used to successfully mimic the 3D organoid microenvironment (72). To examine the efficacy of novel antitumour drugs, Vidal-Crespo *et al* (69) used patient lymph nodes to establish 3D spheroids using the hanging drop method, whereas Ceccato *et al* (73) used human femoral bones to construct a TME of DLBCL-bone marrow. Patient-derived tumour xenografts and NOD. Cg-rkdcscid Il2rgtm1Wjl/SzJ mice were used to establish the PDX mouse model. Subsequently, tumours were removed and grown in bioadhesive polyethylene glycol hydrogels to establish DLBCL 3D organoids (70,74). Similarly, to further explore whether senolytics are effective in humans, the investigators used human tissue explants (including tumour tissues) by *in vitro* culture to demonstrate the efficacy of senolytics (63).

6. Drug mechanisms in senescence-related lymphoma resistance

Chemotherapy resistance associated with an ageing microenvironment. Different chemotherapeutic drugs have

different mechanisms of action. Moderate doses of chemotherapy increase the likelihood of SASP and higher doses can directly lead to cell death (75). The autocrine IL-6 signalling loop is induced when the oncogene RAS is activated, and this autocrine loop enhances OIS (36,47). Gilbert and Hemann (18) used mature Burkitt's lymphoma mouse models to demonstrate that the paracrine factors recombinant IL-6 and Timp-1 in the ageing microenvironment are released into the thymus to resist tumour cell DNA damage, resulting in minimal residual tumour lesions. Researchers have suggested that patients with extranodal NKTCL exhibit primary resistance to anthracycline regimens, mainly because of the overexpression of the *MDR* gene (76). Increasing evidence has confirmed that DOX can induce an ageing microenvironment, leading to lymphoma resistance. For instance, in DLBCL, SIPS can activate SENEX and mediate DOX resistance (33,77). Additional ageing microenvironment-related drug resistance mechanisms in various types of lymphomas need to be further explored.

BTK inhibitor resistance is associated with the ageing microenvironment. Specific inhibitors targeting B-cell receptor-associated kinases (BAKs), such as BTK and PI3K, have revolutionised the treatment of B lymphoid malignancies. Evidence suggests that BAK inhibitors are a class of drugs that modulate the cancer (haematopoietic) microenvironment (78,79). However, at times, ibrutinib alone has a poor effect in the treatment of DH/DE-DLBCL. This may be related to the formation of drug-resistant senescent cells in the TME. Alisertib is a senolytic aurora kinase (AK) inhibitor that functions as a senolytic (80). This can disrupt the escape mechanism of the immune microenvironment and block senescent cells. Thus, a BTK inhibitor combined with an AK inhibitor may overcome drug resistance in DH/DE-DLBCL (54).

Asparaginase inhibits lymphoma progression by promoting cell senescence. In the treatment of certain peripheral T-cell lymphomas (PTCL), such as NKTCL, drug resistance often develops to cyclophosphamide, DOX, vincristine and prednisone (CHOP) regimens containing DOX. Furthermore, asparaginase-containing regimens, such as cisplatin, dexamethasone, gemcitabine and pegaspargase (DDGP) or pegaspargase, gemcitabine and oxaliplatin (P-Gemox) are often chosen by clinicians (81).

This may be because asparaginase does not depend on classical resistance mechanisms; for example, MDR-associated ABC family members lead to drug resistance. Asparagine has long been considered a tumour metabolite (82). It is related to mTORC1 activity and intracellular asparagine can be exchanged with extracellular amino acids, thereby regulating the uptake of amino acids, particularly serine, arginine, and histidine, which are important regulators of amino acid homeostasis, anabolism and the proliferation of cancer cells (83). Because asparaginase, the cornerstone of extranodal NKTCL and acute lymphoblastic leukaemia (ALL) therapy, is irreplaceable, exploring the mechanisms involved in its action is important (84).

Researchers isolated *Rhodospirillum rubrum* L-asparaginase (RrA), a telomerase inhibitor that promotes the senescence of Jurkat cells (a type of T-cell lymphoma cell). RrA cannot inhibit telomerase directly but can downregulate

hTERT expression and induce replicative senescence in lymphoma cells (85,86). The association between cellular senescence and amino acid metabolism involving L-asparaginase is currently unknown. This may be key to future research on L-asparaginase resistance in R/R lymphomas.

Epigenetic drugs reverse senescence-related drug resistance in lymphoma. Decitabine (5-aza-CdR), a DNA methyltransferase inhibitor, was reported to inhibit the progression of anaplastic large cell lymphoma (ALCL) and promote the expression of p16^{INK4A} in the retinoblastoma protein and SA- β -gal pathways (87). This may be a crucial mechanism in decitabine treatment-resistant ALCL (88).

Zeste homologue 2 is a histone methyltransferase enhancer whose aberrant expression directs cells towards the cancer stem cell state by regulating the balance between self-renewal and cell differentiation (89).

Histone acetyltransferases (KATs) have essential roles in various organisms. KAT6A (MOZ or MYST3) and KAT6B (MORF or QKF) belong to the KAT family of oncogenes that inhibit cellular senescence. Allele deletion of KAT6A prolongs the median survival of *Myc* transgenic mice with lymphoma. Selective inhibitors of KAT6B, such as WM-1119, suppress lymphoma development in mice. These results suggest that KAT6A and KAT6B inhibitors may be effective therapeutic agents for lymphoma (90,91).

However, various drugs are still in preclinical stages. Epigenetic modifications involving H3K9me3 were indicated to drive stem cell-like functions in B-cell lymphomas in a senescent model employing *E μ -Myc* transgenic mice. Specifically, H3K9me3 modifications or p53 mutations interfere with cellular senescence in lymphoma and cause cells to re-enter the cell cycle, which manifests as a stem cell-like function in lymphomas with the failure of chemotherapy-induced senescence (32). In addition, senescence-associated epigenetic genes mediated by H3K9me3 in mice helped successfully predict the prognosis of patients with lymphoma (92). Furthermore, RNA modifications may also influence stem cell function. For instance, increased m6A reader insulin-like growth factor 2 mRNA binding protein 2 expression determines the transcriptional level and function of hematopoietic stem cells (HSCs) (93).

Immunotherapeutic drugs regulate senescence-related lymphoma resistance. T-cell immune responses are compromised in ageing environments. B7-H1, a member of the B7-family, is highly expressed in older naïve CD8⁺ T cells and is considered to negatively regulate CD8⁺ T cells. In lymphoma immunotherapy, CD8⁺ CTLs are the main immune cells that attack tumours. The downregulation of CD8⁺ T cells in ageing environments is a critical reason for unsuccessful treatment (94). Adaptive T-cell immunity controls senescence-prone myeloid differentiation factor 88 (MyD88)- or caspase recruitment domain-containing protein 11 (CARD11)-mutant B-cell lymphomas (95).

Programmed cell death protein 1 (PD-1) inhibitors are effective immunotherapeutic drugs that improve the prognosis of patients with relapsed/refractory lymphoma (96). Senescent cells express the immune checkpoint protein PD-1 ligand 1 (PD-L1). PD-L1-containing cells are sensitive to T-cell

surveillance and exhibit resistance even in the presence of SASPs. Blocking PD-L1 and eliminating senescent cells using immune checkpoints represent promising therapeutic strategies (97). Furthermore, PD-1 is highly expressed in the effector memory T cells of older mice, exhibiting proliferative hyporesponsiveness (98). In aged mice, blocking the PD-1/PD-L1 pathway may restore T-cell function (99). Furthermore, a study investigating the reduction in immune-related adverse events (irAEs) caused by immune checkpoint blockade (ICB) reported that anti-PD-1 therapy induces irAE-like multiple organ dysfunction in older mice with tumours, but not in young mice. However, ICB-induced irAEs are mitigated by blocking CD4⁺ T cell-dependent IL-21 or CXCL13 activity and by B-cell depletion (100).

Chemotherapy and radiation therapy induce tumour-cell senescence and contribute to the generation of SASPs, which affect the immune response. Numerous senescent cells secrete excessive amounts of SASP, leading to drug resistance. Chimeric antigen receptor T-cell therapy is a new treatment option to overcome this resistance (101). However, the underlying mechanism remains to be fully elucidated.

Cytokines in the ageing microenvironment are a double-edged sword in lymphoma treatment. These are also regarded as part of the SASP. Specific CTLs lead to the emergence of drug-resistant cancer in the presence of IFN- γ in the TME. In E.G7-OVA murine T-cell lymphoma models, ERK-specific CTLs combine to release IFN- γ into the TME, resulting in the clonal proliferation of resistant cells. Based on these findings, scientists hypothesised that IFN- γ mediates CTL-dependent immunoeediting. ERK-specific CTLs combined with IFN- γ alter the copy number of DNA damage response (53). IL-15 increases CD8⁺ T-cell function by delaying JAK3-STAT5-associated senescence (59). IL-6 reverses DOX resistance in nasal NKTCL by downregulating ABCC4 and inactivating the JAK2/STAT3/NF- κ B/P65 pathway (60). Increased expression of IL-7 in aged mouse T-cell regions mediates the expansion of $\gamma\delta$ 17 T-cell compartments, alters the cellular composition of the $\gamma\delta$ T-cell pool in pLNs and leads to accelerated tumour growth (26).

Other senescence-related mechanisms in lymphoma resistance

Autophagy. Ataxia-telangiectasia mutated (ATM) kinase has a pivotal role in DNA damage response and is a critical molecule in regulating the connection between autophagy and senescence. ATM promotes SASP formation by suppressing selective autophagy of GATA binding protein 4 (102,103). ATM has been identified in mantle cell lymphoma (MCL) as a mutated gene in the 11q22.2 region and engages in crucial interactions with E3 ubiquitin ligase in B cell lymphomas (104,105). ATM deletion induces cell malignancy (106).

Hypoxia-mediated molecules. Hypoxia induces tumour tolerance to radiotherapy and chemotherapy, and promotes malignant biological behaviours, such as tumour-cell growth, invasion and metastasis. The hypoxia-inducible factor 2 α stemness pathway is regulated by MYC and mediated by Nanog and Sox2 to maintain a state of self-renewal in tumour stem cells. The stemness pathway also plays a crucial role in overcoming drug resistance (Fig. 2) (107).

7. Treatment strategies for senescence-mediated lymphoma resistance

Treatment resistance often develops after multi-line chemotherapy. Senotherapeutics may represent a promising therapeutic strategy, as certain senescent cells are reprogrammed and exhibit resistance to treatment. The National Cancer Institute has proposed the 'one-two punch cancer therapy' strategy to first induce senescent cells and then clear such cells in the ageing environment of tumours. For individualised resistant lymphoma, cellular senescence drugs may be chosen in combination with other treatments. For instance, immunotherapy or epigenetic drugs combined with senolytics are more effective in clearing senescent cells (31,32). From the perspective of an ageing environment to overcome drug resistance in lymphoma, it may be concluded that these drugs provide more treatment options for patients with drug-resistant lymphoma.

Hsp90 inhibitors. Heat shock protein 90 (Hsp90) is an oncogene that promotes c-MYC mRNA stability (108), regulates tumour immunology (109) and participates in aberrant metabolism of lymphoma cells (110). Hsp90 inhibitors act as novel senolytic agents (111) that have rapidly developed in preclinical research on lymphomas. They downregulate DNA replication in MCL, indicating a senolytic function (112). Hsp90 inhibitors sensitise lymphoma cells to the chemotherapeutic drugs cisplatin and the BTK inhibitor ibrutinib (113,114). BIIB021, a classic Hsp90 inhibitor, functions as a senolytic agent and overcame multidrug resistance in a preclinical study on lymphomas (115).

In 2015, a phase I clinical trial of KW-2478, a novel Hsp90 inhibitor, reported that 96% of patients with R/R B-cell malignancy temporarily achieved stable disease. Long-term survival outcomes were not assessed. The most common AEs were diarrhoea, fatigue, headache and hypertension. Most patients showed generally good tolerance (116). The phase II study of AUY922 enrolled 14 patients with DLBCL and 6 patients with PTCL. Across the whole group, the response rate stood at 10%, encompassing complete response (CR) in 7% of DLBCL cases and partial response (PR) in 17% of patients with PTCL. In the majority of cases, the toxicity profile appeared to be satisfactory (117).

Hsp90 inhibitors have demonstrated favorable efficacy and tolerable side effects in a subset of patients with R/R lymphoma, with significant interindividual variability. However, the majority of patients experience disease progression after administration, indicating that monotherapy with Hsp90 inhibitors may not promptly control disease progression, necessitating combination with other drugs to enhance therapeutic efficacy. However, as they are agents targeting cellular senescence, further investigation is needed to elucidate the therapeutic biomarkers and long-term survival rates in patients treated with Hsp90 inhibitors.

AK inhibitors. AK inhibitors are promising inducers of aneuploidy and senescence in patients with haematological malignancies. Aurora kinase A (AURKA) is a key enzyme involved in cell-cycle regulation (118), which may be applied to the first step in 'one-two punch therapy' to induce cellular

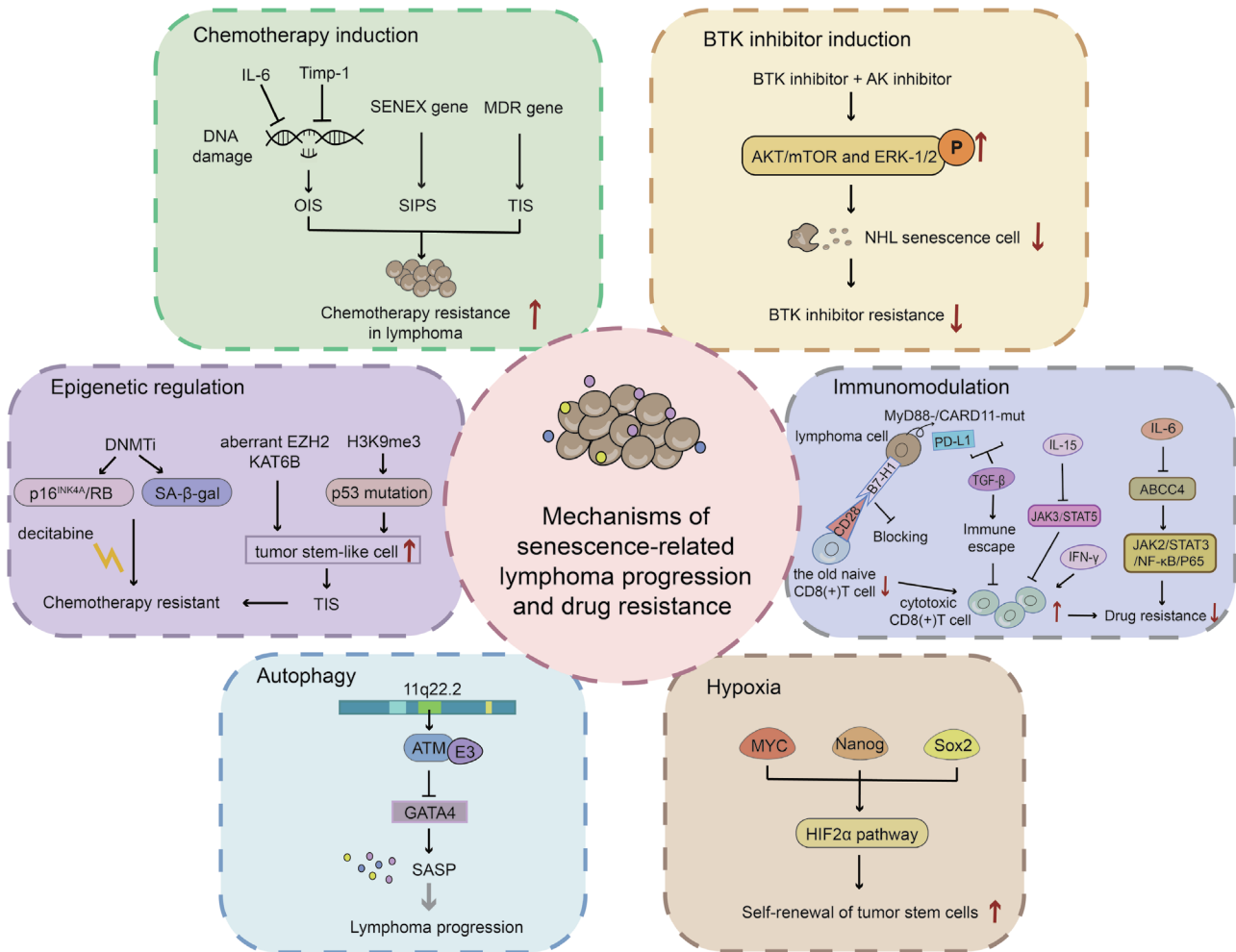


Figure 2. Mechanisms of senescence-associated lymphoma progression and drug resistance. Multiple mechanisms of lymphomagenesis and drug resistance participate in the ageing environment, including DNA damage caused by chemotherapy drugs, BTK inhibitor resistance mediated by signalling pathways, epigenetic regulation inducing TIS, immune regulation restraining drug resistance in lymphoma, autophagy mediating lymphoma progression, and hypoxia promoting lymphoma stem cell self-renewal. SASP, senescent-associated secretory phenotype; SA- β -gal, senescence-associated β -galactosidase; TIS, therapy-induced senescence; SIPS, stress-induced premature senescence; OIS, oncogene-induced senescence; Timp-1, tissue inhibitor of metalloproteinases-1; BTK, Bruton's tyrosine kinase; AK, aurora kinase; NHL, non-Hodgkin lymphoma; DNMTi, DNA methyltransferase inhibitors; EZH2, enhancer of zeste homolog 2; H3K9me3, trimethylation of histone H3 lysine 9; PD-L1, programmed cell death 1 ligand 1; ABCC4, ATP-binding cassette transporter 4; ATM, ataxia-telangiectasia mutated; E3, ubiquitin ligase; GATA4, GATA binding protein 4.

senescence. In preclinical studies, AURKA was found to be overexpressed in various haematological malignancies, including DH/DE-DLBCL (118), multiple myeloma (MM) (119) and NKTCL (120). MK-8745 (a small-molecule AURKA inhibitor) significantly increased apoptosis of NKTCL cells and induced cell-cycle arrest (120).

Currently, AK inhibitors are in the clinical trial stage for relapsed/refractory lymphomas. In 2014, monotherapy with the AURKA inhibitor alisertib achieved a clinical response in a phase II clinical trial for a total of 48 patients, including those with aggressive B- and T-cell lymphomas. The objective response rate (ORR) of 48 patients in this study was 27%. Most common AEs were neutropenia and leukopenia (121). In a study from 2018, an AURKA inhibitor combined with rituximab or rituximab/vincristine showed synergistic effects in a phase I clinical trial of 45 patients in total with aggressive B-cell lymphoma. It is worth noting that among the 45 patients, the regimen only demonstrated activity in 20 patients with non-germinal center B-cell (non-GCB)

DLBCL. Out of 20 patients, 9 (45%) showed a response (4 CRs, 5 PRs). The most common AE was neutropenia. Of note, all of the patients with non-GCB DLBCL showed good tolerance (122).

Overall, AK inhibitors are promising senolytics for the development of new therapies for patients with lymphoma. However, there is currently limited data on AK inhibitors specifically targeting subtypes of lymphoma, with numerous studies being descriptive clinical investigations lacking statistical and evidence-based medicine support (121,122). Further research is warranted to provide more comprehensive insight into this area.

Proteasome inhibitors. Bortezomib is a proteasome inhibitor and a senolytic agent. The primary mechanism of action of bortezomib is to suppress chymotrypsin-like sites in 26S protease, which then promotes cell-cycle arrest and, ultimately, apoptosis (123). Because endoplasmic reticulum (ER) homeostasis is strictly controlled, the level of ER stress beyond

a certain point can change from a pro-survival pathway to a pro-apoptotic pathway, ultimately leading to ER stress-induced apoptosis. Bortezomib is a clinically available senolytic drug that targets ER homeostasis (62) and has been approved as a second-line treatment for MCL and MM (123,124).

Furthermore, in 2018, phase III clinical trials investigating bortezomib in 487 patients newly diagnosed with stage II-IV MCL reported a significantly prolonged median overall survival (OS) in the bortezomib treatment arms compared to those without bortezomib (90.7 vs. 55.7 months). AEs occurred in 42 and 57% of patients who died in the bortezomib and non-bortezomib groups, respectively, with progressive disease emerging as the predominant cause of mortality (125). In 2022, in a phase III clinical study, 209 patients with T-cell lymphoblastic lymphoma (T-LL) were included, comparing those not on bortezomib to those on bortezomib. The four-year OS rate of patients with T-LL stood at 89.5% when treated with bortezomib, in contrast to 78.3% in the absence of bortezomib. The general toxicity rates of grade 3 and above were comparable in both groups (126).

In summary, the safety profile of bortezomib was found to be well-managed and predictable. These findings provided evidence for the efficacy of bortezomib as an active therapeutic agent in MCL and T-LL.

Pathway inhibitors. Senescence-associated pathway inhibitors for the treatment of R/R lymphoma are currently undergoing clinical trials. Below, the pathway inhibitors currently under study in this field are summarised.

mTOR inhibitors. mTOR inhibitors have been comprehensively studied to extend the lifespan. mTOR affects T- and B-lymphocyte differentiation, function and cell death (127). In a phase I/II clinical trial investigating the mTOR inhibitor temsirolimus in combination with lenalidomide for R/R lymphomas, an ORR of 26% (13% CR) was achieved for patients with DLBCL. Among patients with classical HL (cHL), many of whom had relapsed following both brentuximab vedotin and autologous stem cell transplantation, the ORR was 80% (35% CR). Grade 3/4 hematologic AEs were frequent and included anemia, lymphopenia, neutropenia, thrombocytopenia and leucocytosis (128). The combination regimen involving temsirolimus and lenalidomide proved to be viable and showed promising efficacy in the treatment of lymphoma.

Notch pathway inhibitors. Advanced T-cell leukaemia and B-cell lymphoma may be accompanied by *NOTCH1* mutations. Notch signalling cascades crosstalk with Wnt signalling and maintain stem-cell characteristics in tumour stem cells. Small molecule γ secretase inhibitors (such as AL101, MRK-560 and nirogacestat) and antibody-based biologics targeting Notch ligands or receptors (such as ABT-165, AMG 119, rovalpituzumab and tesirine) have been developed into drugs (57). The Notch pathway inhibitor crenigacestat was designed for use in a phase I clinical trial of R/R T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma. A total of 36 patients were enrolled, with a median event-free survival of 1.18 months. The most common AEs occurring in $\geq 30\%$ of patients at any grade were diarrhea, vomiting and nausea (129). In summary, findings from this phase I trial suggest that, while there is some indication of clinical efficacy,

the advancement of crenigacestat for T-ALL/T-LBL treatment may be constrained by gastrointestinal toxicities.

JAK/STAT inhibitors. The JAK/STAT signalling pathway is closely associated with senescence-related resistant lymphoma. SB1518 is a selective inhibitor of JAK2, a member of the JAK family, demonstrating its function as an antitumour agent in mutant JAK2-driven lymphocyte lines (130). A phase II clinical trial with the JAK inhibitor ruxolitinib was performed in 45 patients with PTCL and 7 patients with mycosis fungoides. The ORR and clinical benefit rate were 25 and 35%, respectively. AEs predominantly encompassed cytopenias, within the controllable range (131). In addition, a phase II clinical trial involving ruxolitinib was conducted for R/R cHL. The median progression-free survival was 3.6 months and the estimated 1-year OS rate was 50.6% (median OS not reached). A single grade IV AE (7.1%) indicated the toxicity was tolerated (132). In short, ruxolitinib monotherapy appears to have limited efficacy. Focusing on combined treatments is warranted to improve the efficiency and durability of responses.

Bcl-2 family protein inhibitors. The BCL-2 family of protein inhibitors has achieved success in the treatment of lymphoma. The use of these inhibitors has also been associated with senescence-associated drug resistance in lymphomas, particularly relapsed or refractory lymphomas. Bcl-2 family inhibitor navitoclax (ABT263, a BCL-xL/BCL-2 inhibitor) has senolytic functions in R/R ALL or LBL, and senescent bone marrow HSCs (133,134). In a phase I study of the selective BCL-2 inhibitor, the efficacy of venetoclax in combination with low-dose navitoclax and chemotherapy was evaluated in pediatric and adult patients with R/R ALL/LBL. The ORR was 60% and the treatment was well tolerated by patients (131). In conclusion, dual inhibition of BCL-2 and BCL-XL by venetoclax and narvesone in combination with chemotherapy is associated with significant response rates and a good safety profile, which is a suitable treatment option for R/R ALL or LBL.

Immunoadjuvant therapy. PD-1/PD-L1 inhibitors restore T-cell function in aged mice. From the perspective of the ageing microenvironment, PD-1 inhibitors used to treat relapsed and refractory T-cell lymphomas have achieved good treatment results in preclinical studies (99). In *MyD88*- or *CARD11*-mutant B-cell lymphomas, senescent tumour cells express high levels of PD-L1, thus mediating age-related immune evasion (95). In recent years, PD-1 inhibitors have been used to treat various relapsed or refractory lymphomas, such as R/R cHL (135) and R/R follicular lymphoma (136). However, PD-1 inhibitors targeting senescent lymphoma cells have not been studied in clinical trials.

Reversing T-cell senescence is another means of treating senescence-related drug-resistant cells. Studies have shown that T cells with mitochondrial dysfunction, owing to mitochondrial transcription factor A (TFAM) deficiency, can act as senescence accelerators. Blocking the TNF- α signalling pathway with nicotinamide adenine dinucleotide precursors may partially prevent premature senescence in TFAM-deficient mice (28). From the perspective of clinical transformation, the NAD⁺ precursor nicotinamide riboside is a promising drug to reverse

Table I. Applications of treatments in senescence-related lymphoma resistance.

Classification	Drug name	Target	Phase	NCT number	Diseases	(Refs.)
Senolytics	KW-2478	Hsp90	Phase I/	NCT00457782/	B cell	(116,117)
	AUY922	inhibitor	Phase II	NCT01485536	malignancies/NHL	
	Bortezomib	Proteasome	Phase III/	NCT00722137/	MCL/T-LL	(124,125)
		inhibitor	Phase III	NCT02112916		
	Navitoclax (ABT263)	Bcl-2/Bcl-xL	Phase I	NCT03181126	R/R ALL or LL	(132)
	SSK1	β -galactosidase	Preclinical	-	Targeting senescent cells	(143)
	JQ1/ RVX2135	BETi	Preclinical	-	Myc-induced lymphoma mice	(144)
Pathway inhibitors	Alisertib	Aurora kinase A inhibitor	Phase I/II	NCT01397825/ NCT00807495	R/R aggressive B-cell and T-cell lymphoma	(121,122)
	Temsirolimus	mTOR inhibitor	Phase I/ Phase II	NCT01076543	R/R lymphoma (including DLBCL/FL/cHL)	(127)
	Crenigacestat	NOTCH inhibitor	Phase I	NCT02518113	R/R T-ALL/T-LBL	(128)
	Ruxolitinib	JAK inhibitor	Phase II/ Phase II	NCT02974647/ NCT02164500	R/R PTCL/cHL	(130,131)
Immunoadjuvant therapy	PD-1 inhibitor	PD-1 inhibitor	Preclinical	-	T-cell lymphomas/ B-cell lymphomas	(95,99)
	NAD+ precursor	NAD+ precursor	Preclinical	-	Targeting senescent T-cells	(28)
	nicotinamide riboside	nicotinamide riboside				

R/R, relapsed or refractory; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; cHL, classical Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; HSP, heat shock protein; PD-1, programmed cell death 1; BETi, bromodomain and extra-terminal inhibitors; NCT, National Clinical Trials.

immune-cell or lymphoma-cell senescence and may represent an emerging treatment for drug resistance in lymphoma.

Other promising senolytics. Alternative medicines, particularly Traditional Chinese Medicines (TCM), have an important role in lymphoma ageing-related drug resistance by regulating immune function, improving the TME and regulating antioxidant and anti-inflammatory pathways. However, TCM therapy requires an individualised regimen and should be combined with modern medical therapy regimens in clinical treatment to achieve the best therapeutic effect (137,138). For instance, dasatinib combined with quercetin as a classic senolytic agent is effective in the senescence-associated treatment of solid tumours (75,139,140). Dasatinib is a vital tyrosine kinase inhibitor used for targeted leukaemia and lymphoma therapy (141,142). Quercetin, a TCM drug, also exhibits anti-lymphoma effects (143). When combined with dasatinib, it may serve as an efficacious senolytic agent in patients with clinically resistant lymphoma. Further research on the use of TCM for the treatment of senescence-related drug resistance in lymphomas is necessary.

The β -gal-targeting drug SSK1 can selectively clear senescent cells and may represent a novel drug to intervene in senescence-related drug resistance in lymphoma cases (144).

Bromodomain and extra-terminal inhibitors (JQ1/RVX2135) have been found to synergise with ATR inhibitors (AZ20 and VE-821) to induce DNA damage, apoptosis, SASP pathways and ER stress in Myc-induced lymphoma cells in preclinical research (28) and represent promising senolytic agents for ageing-associated drug resistance in lymphoma treatment (Table I, Fig. 3).

8. Conclusion and perspectives

In the application of the 'one-two punch cancer therapy', it is necessary to distinguish the differentiation outcome of senescent cells at different periods. In the early stages, cells gradually become senescent and move towards cell death (through processes such as apoptosis, ferroptosis and cuproptosis). In later stages, a large number of senescent cells form an ageing microenvironment and move towards treatment resistance through SASP reprogramming. The

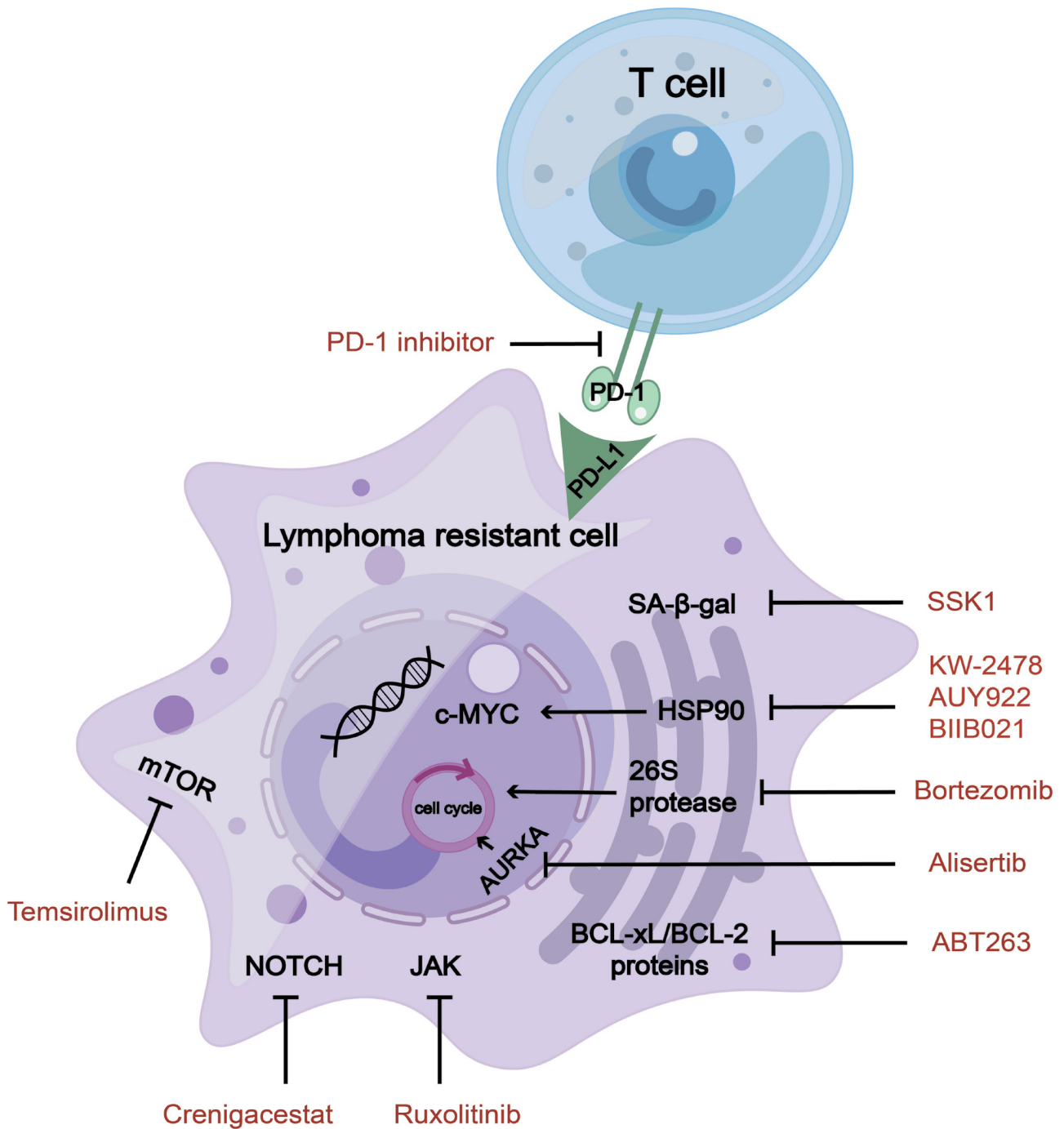


Figure 3. Inhibitors that target senescence-related drug-resistant lymphoma cells. Manipulating the target inhibitors of SA-β-gal/HSP90/26S protease/AURKA/Bcl-2/Bcl-xL and mTOR/NOTCH/JAK pathway inhibitors has been shown to be effective in treating lymphoma-resistant cells. In the ageing environment of lymphoma, PD-1 inhibitors restrain the combination of T-cells and drug-resistant cells. SA-β-gal, senescence-associated β-galactosidase; HSP, heat shock protein; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; AURKA, aurora kinase A.

senescent messaging secretome has an important role in the mechanisms underlying chemotherapy/radiotherapy, targeted therapy and immunotherapy resistance in lymphomas. In the early stages, senescent cells can be treated with pro-cellular senescence drugs, and in the later stages, drug-resistant senescent cells can be removed using senolytics or SASP inhibitors in conjunction with SASP reprogramming. Furthermore, senolytics combined with immunotherapy and epigenetic drugs may be more effective for patients with relapsed or refractory lymphoma.

It should be noted that the type of lymphoma and specific circumstances of the patient may influence the choice of treatment. Therefore, the treatment of lymphoma often requires individualised and condition-based decision-making, including the consideration of factors such as senescence-related drug resistance. Currently, the development of several senolytic drugs is limited to preclinical studies and clinical trials. The heterogeneity of senescent cells is a major obstacle to their clinical transformation. However, the development of senescence-associated targeted drugs may lead

to important breakthroughs in overcoming lymphoma drug resistance.

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Availability of data and materials

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Authors' contributions

Investigation: YZ, JC, QH and SQ. Software: YG and MM. Supervision: MZ, XZ and QC. Writing-original draft: YZ and JC. Writing-review and editing: QH, SQ, ZW, QY, WS, LD, ZS, XZ and QC. All of the authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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